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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/237,291	01/25/99	YOUNG J	SYS-2068

001095
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EXAMINER	
SCHMIDT, M	
ART UNIT	**PAPER NUMBER**
1635	12
DATE MAILED:	01/04/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/237,291	Young et al.
Examiner	**Group Art Unit**
Schmidt	1635

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 10/12/00.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 18-20, 23-27, 31-35, 37-44, 46-47 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 18-20, 23-27, 31-35, 37-44, 46-47 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Notice of References Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

1. Claims 18-20, 23-27, 31-35, 37-44 and 46-47 are pending. This Official Action is in response to the remarks filed 10/12/00, Paper 11.

Claim Rejections - 35 USC § 103

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 18-20, 23-27, 31-35, 37-44 and 46-51 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al. (US Patent 5,665,557) , Nakahata (US Patent 5,861,315), Hoffman et al. (US Patent 5,744,361), Fei et al. (US Patent 5,635,387) or Davis et al. (US Patent 5,599,703), in view of Ku et al, Kobayashi et al, Ramsfjell et al (IDS Reference AK), Ohmizono et al, Szilvassy et al, Escary et al., or Bodine et al, and further in view of Tushinski et al (IDS Reference AN), Fletcher et al., Bello-Fernandez et al, Hatzfeld et al., and Hanenberg et al. (Nature Medicine Vol. 2, No. 8) or Henenberg et al. (IDS Reference AR) for the same reasons of record as set forth in the Official Action on the Merits mailed 04/10/00.

Applicant's arguments filed 10/12/00 have been fully considered but they are not persuasive.

Applicant argues (1) that the 35 U.S.C. 103 (a) rejection was made after Examiner engaged in "impermissible, hindsight reconstruction to pick and choose among the prior art in order to try to fashion a rejection of the claimed invention." Applicant further argues (2) that "the question with respect to patentability of the claimed invention is not whether a person of ordinary skill in the art would have had a reasonable expectation of success with respect to individual components of the claimed invention, but whether that person would have had a reasonable expectation of success with regard to the combination of all of the components of the invention, i.e. whether the invention as a whole was obvious. The Examiner has not shown that the invention as a whole invention... was obvious." Further Applicant notes that (3) Examiner previously wrote in a prior Office Action that "There is a high level of unpredictability in the transgenic stem cell art for expression of transgenes in cultured stem cells." Thus Applicant asserts that "given this unpredictability, a person of ordinary skill in the art would not have had a reasonable expectation of success with respect to the claimed invention as a whole." Applicant writes that (4) "Examiner has not shown how the cited references teach the concentration ranges recited in the claims. The Examiner has cited references where certain factors in the claims were used at certain concentrations, but she has made no showing of how the references teach the recited ranges of concentrations." Finally, Applicant notes (5) that "claims 35, 44 and 51 are directed to CD34+ thy-1+Lin- HSCs. The Examiner has not shown how the cited references teach the genetic modification of these particular HSCs in the presence of the factors and at the concentration ranges recited in the claims."

In response to these assertions, Examiner cites that following illustrative examples from the cited art that one skilled in the art would have been motivated to specifically use CD34+Thy-1+Lin- HSCs: (a) U.S. Patent 5,750,397 col. 3, para. 3; (b) U.S. Patent 5,744,361 col. 4, lines 4-5; (c) U.S. Patent 5,665,557 col. 3, para. 5 and col. 5, lines 49-61. These references teach that CD34+Thy-1+Lin- are common attributes of HSCs grown in cell culture since these characteristics are used in the isolation process of HSCs from the source tissue. The motivation of one of ordinary skill in the art to grow said cells at specific growth factor concentration ranges recited in the claims is taught by the combination of these and the other prior art references cited.

Specifically, the broad claim 18 recites adding an effective amount of a **mpl** ligand and a **flt3** ligand (**FL**) each at about 0.1 ng/mL to about 500 ng/mL. Claims 23 and 37 recite **TPO**, **FL** and **IL-6** at about 0.1 ng/mL to about 500 ng/mL. Dependent claims to claim 18 add **c-kit** from about 5ng/mL to about 200ng/mL, **IL3** from about 5ng/mL to about 200ng/mL. Dependent claims to claims 23 add **LIF** at about 5ng/mL to about 200ng/mL, **c-kit** from about 5ng/mL to about 200ng/mL, **IL3** from about 10ng/mL to about 100ng/mL, and further specify **TPO** at a concentration of about 5ng/mL to about 200 ng/mL and **IL-6** in the range of about 10ng/mL to about 100ng/mL. Dependent claims to claim 37 further specify the following concentrations: **TPO**, **FL** and **IL-6** all at about 5ng/mL to 200ng/mL; where the concentration of **IL3** is about 10ng/mL to about 100ng/mL; where the concentration of **c-kit** is in the range of 5ng/mL to about 200ng/mL; and where the amounts of **TPO** and **FL** and each in the range of about 5ng/mL to about 200ng/mL and **IL6** is about 10ng/mL to about 100ng/mL.

As taught in the prior Official Action mailed 4/10/00, pages 3-4, the prior art teaches the use of all of the claimed factors for growth of HSCs. Although no one reference may teach the specific combination of cytokines instantly claimed, the art as a whole clearly teaches that specific composition of HSCs, even selected CD34+Thy-1+Lin- HSCs, vary based on the point at which they were isolated and the growth conditions used (see U.S. Patent 5,665,557 col. 2, para. 5, for instance), which causes differential expression of genes which lead the cells down different paths of growth and thus different outcomes. The use of different cytokine concentration ranges is thus a result of the variance among the isolated cell populations. The story is increasingly complex when one of ordinary skill in the art transforms a population of cells for expressing a transgenic gene so that the cells maintain a certain state of differentiation and gene expression level, or so that the cells will be useful as genetically transformed cells for which the methods of culturing HSCs are generally used for. One of ordinary skill in the art was aware at the time of the instant invention of the motivation to use those cytokines taught in the art on different populations of HSCs in different cytokine concentrations as taught such that the slightly different types of cells were tested with different concentrations of growth factors to optimize the growth (each reference cited teaches unique circumstances to their cell population). The use of ranges of growth factor concentrations of these specific factors was not new either. The specific references cited teach application of each of the claimed factors in comparable ratios absent evidence to the contrary (some of the references teach the Units/mL of the factors, which appear to be in the claimed ranges in view of the open "comprising" language, the "about" language and the

"effective amount" language, thus suggesting that since the claim language is open and the references teach effective amounts, the amounts taught in the references read on the instant claims). It was thus argued, that as broadly claimed, the combination of the cited references provides one of ordinary skill in the art with the requisite motivation and expectation of success to make and use the invention as claimed, ie. it was obvious to one of ordinary skill in the art to use the claimed combinations of factors as claimed.

Further, Hanenberg et al. was relied upon to teach the use of fibronectin as a means of optimizing retroviral gene transfer in HSCs and Fletcher et al. was relied upon to teach the use of LIF in the range of 0-1000U/mL to teach that LIF appears to primarily "delay... stem cell commitment to differentiation (p. 844)." These two thus teach optimization of general HSC protocols for the benefits claimed. One of ordinary skill in the art would have had an expectation to see some of the claimed benefits by use of these products in the methods as instantly claimed.

Therefore, it was not by hindsight reconstruction that a rejection was fashioned to read on the instant claimed invention. On the contrary, the cited references broadly teach the use of all the claimed factors for optimized growth of HSCs as cited above and in concentrations which read on the claimed concentrations in view of the open language of the claimed methods. The motivation was taught in the cited references to isolation and grow HSCs in cultures which apply the claimed factors for the functions claimed and having the steps of retrovirally transducing the cells.

As applicant points out, the initial Official Action on the merits mailed 5/12/99 cites the unpredictability in the transgenic stem cell art for expression of transgenes in cultured stem cells.

However, the claims at the time of that action broadly claimed any method for promoting the expansion of hematopoietic stem cells in culture and the unpredictability focused on the unpredictability of transforming any hemopoietic cell in the art from any species as broadly claimed. Upon amendment of the claims to specify human cells and a review of the pertinent art, the enablement rejection was withdrawn in view of the instant rejections over the methods of genetically modifying HSCs. As argued above, the art is replete with examples using various cytokine concentrations (which read on the claimed concentrations) such that it would have been obvious at the time the invention was made to practice the invention claimed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
January 1, 2001

REMY YUCEL, PH.D
PRIMARY EXAMINER